IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant:	Randall W. Nelson et al.
Serial No.:	09/024,988
Filing Date:	February 17, 1998
Title:	MASS SPECTROMETRIC IMMUNOASSAY
Examiner:	Anne L. Holleran
Art Unit:	1642

TO: Mail Stop APPEAL BRIEF-PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANT'S BRIEF
PURSUANT TO 37 C.F.R. § 41.37

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(Submitted in Triplicate)

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Dear Commissioner:

Appellant appeals the decision of the Examiner finally rejecting all of the claims pending in the present application, namely claims 31, 33, 40 and 48-50. A Notice of Appeal was filed by Appellant on September 11, 2006. Appellant is filing this Brief on March 12, 2006 along with a four month extension request. **This appeal is being submitted in triplicate.**

I. REAL PARTY IN INTEREST

Intrinsic Bioprobes, Inc. is the real party in interest in the subject patent application, by virtue of an Assignment from inventors Randall W. Nelson, Peter Williams, and Jennifer Reeve Krone to Intrinsic Bioprobes, Inc. (recorded on June 25, 2004 at Reel 015501, Frame 0527).

II. RELATED APPEALS AND INTERFERENCES

One other appeal is currently known that may directly affect, be directly affected by, or have a bearing on the decision to be rendered by the Board of Patent Appeals and Interferences in the present Appeal. That appeal is currently pending in relation to Serial No. 09/808,314.

III. STATUS OF CLAIMS

Claims 32, 34-39, and 42-47 are withdrawn.

Claims 1-30 and 41 are cancelled.

Claims 31, 33, 40, and 48-50 are pending in the application.

Claims 31, 33, 40, and 48-50 stand rejected under 35 U.S.C. § 103(a) and are appealed herein.

IV. STATUS OF AMENDMENTS

An amendment was filed after the Examiner's Final Office Action, amending claims 31, 33, 48, and 49 and canceling claim 41, without prejudice or disclaimer. The amendment was not entered by the Examiner because the Examiner deemed that the amendment raised new issues that would require further consideration and/or search. In particular, the Examiner stated that "a new issue under 35 USC 112, second paragraph is raised by the amendment, because claims 33 and 49 have been amended to recite 'further consists'" and that "Because consisting of is closed language and because the independent claims have been amended to be methods 'consisting of' it is not clear how a dependent claim may 'further consist'". In addition, the Examiner stated that "the amendment of claim 33 presents a new issue under 35 USC 112, second paragraph, because claim 40, which is dependent on claim 33, contains the transitional phrase 'comprising', whereas claim 33 has been amended to recite 'consists of'".

Appellant traverses the examiner's contention that Appellant's amendments after final rejection raise new issues under 35 USC 112. Appellant's arguments traversing the examiner's contention are detailed below in Appellant's "Argument" section of its brief.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The pending application relates to a method for quantifying the relative amount of one or more analytes (antigens or antibodies) present in a specimen. Antigens or antibodies contained within a specimen are qualitatively and quantitatively determined by utilizing an antibody or antigen to capture and isolate another antigen or antibody, respectively, from its surroundings and then mass spectrometrically analyzing the isolated antibody or antigen after releasing it from the capturing agent. The specificity of the antibody-antigen reaction coupled with the ability of the mass spectrometer to separate and unequivocally identify the captured and isolated antibody or antigen by its mass-to-charge ratio from other molecules that may accompany it lends to two dimensions of specificity. (See specification, pg. 5, lines 21-31).

The quantitative analysis utilizes standard preparations containing known concentrations of the analyte for calibration. Because it is difficult to control the analytical conditions sufficiently well to ensure constant mass spectrometric response for constant analyte concentration in different samples, at least one internal reference species is introduced to the sample prior to incubation with the affinity reagent. The internal reference species may be added to the analytical system being assayed or it may be intrinsic thereto. The internal reference species is captured, isolated and mass spectrometrically analyzed simultaneously with the analyte thereby serving to calibrate the analytical conditions from one analysis to another because both the analyte and internal reference species respond identically to changes in these conditions. (See specification, pg. 24, lines 23-32 and pg. 25, lines 1-5).

The affinity reagent must contain an affinant that will specifically capture or bind with the internal reference species. (See specification, pg. 25, lines 6-7). The internal reference species is preferably a modified variant of the analyte. An affinant that can capture the analyte can usually also capture the modified variant because the modification shifts the molecular weight of the antibody or antigen without destroying its affinity. Where the internal reference species is not a modified variant of the analyte, another immuno chemical affinity group must be present in the affinity reagent in order to simultaneously capture and isolate the internal reference species along side the analyte. It may be desirable for a protein that is not an antibody to be used

as an internal reference standard in an analysis of an antibody species. In such a situation, the affinity reagent would be prepared with two classes of molecules, an antibody specific for the protein and an antigen for which the analyte is specific. (See specification, pg. 25, lines 15-30).

Applicants' claimed method for quantifying the relative amount of one or more analytes present in a specimen includes combining the specimen with a known amount of internal reference species if the specimen does not already contain one, capturing and isolating at least one of the analytes and the internal reference species where the capturing and isolating step includes a substep of combining the internal reference species containing specimen with an affinity reagent, and quantifying the analyte or analytes in which the quantifying step consists of using matrix-assisted laser desorption/ionization (MALDI) to resolve distinct signals for the analyte and the internal reference species to determine the ratio of the analyte signal to the internal reference species signal. (See claim 31). The quantifying step includes using a working curve analysis that includes the steps of making a plurality of standard preparations, each containing a known but differing concentration of the analyte and each containing a known concentration of IRS, obtaining respective mass spectra of each of the plurality of standard preparations, normalizing each of the mass spectra from the plurality of standard preparations by dividing each mass spectrum by the IRS signal within the mass spectrum, creating a working curve by equating the normalized analyte signals to the analyte concentration of the plurality of standard preparations, obtaining a mass spectrum for the IRS-containing specimen, normalizing the mass spectrum of the IRS-containing specimen by dividing the IRS signal within the mass spectrum, and quantifying the concentration of the analyte in the specimen using the working curve. (See claim 33 and 36).

In addition, the claims pending on appeal are outlined below along with specific minimum references to the specification of the patent application and additional support may be present in the specification for various elements.

31. A method for quantifying an analyte in a specimen, said method comprising the steps of: *(pg. 24, lines 21-22)*

a. combining said specimen with an internal reference species (IRS) if the specimen of known concentration, in order to calibrate all subsequent steps; whereby said combination is referred to as an IRS-containing specimen; *(pg. 24, lines 24-32 to pg. 25, line 1, and Example 1, pgs. 39-41)*

b. combining said IRS-containing specimen with an affinity reagent, capturing and isolating said analyte and said IRS, wherein said IRS is a modified analyte with shifted molecular weight which binds to said affinity reagent; *(pg. 25, lines 6-30, and Example 1, pgs. 39-41)*

c. analyzing and quantifying said analyte wherein analyzing and quantifying comprises using matrix-assisted laser desorption/ionization (MALDI) to resolve distinct signals for said analyte and said IRS to determine the ratio of the analyte signal to the IRS signal. *(pg. 25, lines 1-5, pg. 26, lines 14-20, pg. 29, lines 27-30 to pg. 30, lines 1-17 and Example 1, pgs. 41-43)*

33. A method according to claim 31, in which said quantifying step further comprises working curve analysis. *(pg. 30, lines 18-33 to pg. 32, lines 277 and Example 1, pgs. 39-43)*

40. A method according to claim 33, in which said working curve analysis comprises substeps of:

a. making a plurality of standard preparations, each containing a known but differing concentration of the analyte and each containing a known concentration of IRS; *(pg. 32, lines1-20)*

b. obtaining respective mass spectra of each of the plurality of standard preparations; *(pg. 32, lines 1-20)*

c. normalizing each of the mass spectra from the plurality of standard preparations by dividing each mass spectrum by the IRS signal within the mass spectrum; *(pg. 32, lines 1-20)*

d. creating a working curve by equating the normalized analyte signals to the analyte concentration of the plurality of standard preparations; *(pg. 32, lines 1-20)*

e. obtaining a mass spectrum for the IRS-containing specimen; *(pg. 32, lines 22-28)*

f. normalizing the mass spectrum of the IRS-containing specimen by dividing by the IRS signal within the mass spectrum; *(pg. 32, lines 22-28)* and

g. quantifying the concentration of the analyte in the specimen using the working curve. *(pg. 32, lines 22-28)*

48. A method for quantifying a protein in a specimen, said method comprising the steps of: *(pg. 24, lines 21-22)*

a. combining said specimen with an internal reference species (IRS) if the specimen of known concentration, in order to calibrate all subsequent steps; whereby said combination is referred to as an IRS-containing specimen; *(pg. 24, lines 24-32 to pg. 25, line 1, and Example 1, pgs. 39-41)*

b. combining said IRS-containing specimen with an affinity reagent, capturing and isolating said protein and said IRS, wherein said IRS is a modified protein with shifted molecular weight which binds to said affinity reagent; *(pg. 25, lines 6-30, and Example 1, pgs. 39-41)*

c. analyzing and quantifying said protein wherein analyzing and quantifying comprises using matrix-assisted laser desorption/ionization (MALDI) to resolve distinct signals for said protein and said IRS to determine the ratio of the protein signal to the IRS signal. *(pg. 25, lines 1-5, pg. 26, lines 14-20, pg. 29, lines 27-30 to pg. 30, lines 1-17 and Example 1, pgs. 41-43)*

49. A method according to claim 48, in which said quantifying step further comprises working curve analysis. *(pg. 30, lines 18-33 to pg. 32, lines 277 and Example 1, pgs. 39-43)*

50. A method according to claim 49, in which said working curve analysis comprises substeps of:

a. making a plurality of standard preparations, each containing a known but differing concentration of the protein and each containing a known concentration of IRS; *(pg. 32, lines1-20)*

b. obtaining respective mass spectra of each of the plurality of standard preparations; *(pg. 32, lines 1-20)*

c. normalizing each of the mass spectra from the plurality of standard preparations by dividing each mass spectrum by the IRS signal within the mass spectrum; *(pg. 32, lines 1-20)*

d. creating a working curve by equating the normalized protein signals to the protein concentration of the plurality of standard preparations; *(pg. 32, lines 1-20)*

e. obtaining a mass spectrum for the IRS-containing specimen; *(pg. 32, lines 22-28)*

f. normalizing the mass spectrum of the IRS-containing specimen by dividing by the IRS signal within the mass spectrum; *(pg. 32, lines 22-28)* and

g. quantifying the concentration of the protein in the specimen using the working curve. *(pg. 32, lines 22-28)*

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 31, 33, 40, and 48-50 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Duncan (Duncan, M.W. et al., Rapid Communications in Mass Spectrometry, 7:1090-1094, 1993) in view of Nuwaysir (Nuwaysir, L.M. et al. J. Am. Soc. Mass Spectrom., 4:662-669, 1993).

Claims 31, 33, 40, 48, 49 and 50 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Duncan in view of Hutchens, U.S. Patent No. 6,528,320 (hereafter "Hutchens").

VII. ARGUMENT

A. Applicant's Amendments After Final Do Not Raise New Issues Under 35 USC 112

In asserting that Applicant's amendments made after final rejection raised new issues under 25 USC 112, the Examiner stated that "a new issue under 35 USC 112, second paragraph is raised by the amendment, because claims 33 and 49 have been amended to recite 'further consists'" and that "Because consisting of is closed language and because the independent claims have been amended to be methods 'consisting of' it is not clear how a dependent claim may 'further consist'". In addition, the Examiner stated that "the amendment of claim 33 presents a new issue under 35 USC 112, second paragraph, because claim 40, which is dependent on claim 33, contains the transitional phrase 'comprising', whereas claim 33 has been amended to recite 'consists of'". (See pg. 2 of Examiner's Advisory Action dated Oct. 13, 2006).

The Manual of Patent Examining Procedure explains the difference between the terms "comprise" and "consist" in patent law as follows:

> The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps.
>
> The transitional phrase "consisting of" excludes any element, step, or ingredient not specified in that claim.

Patent and Trademark Office, Department of Commerce, Manual of Patent examining procedure. Sec. 2111.03 (Eight Edition, Revision 5, August 2006).

Applicants claims amended after final read as follows:

Claim 31. (currently amended): A method for quantifying an analyte in a specimen, said method ~~comprising the steps~~ consisting of:

a) combining said specimen with an internal references species (IRS) of known concentration, in order to calibrate all subsequent steps; whereby said combination is referred to as an IRS-containing specimen;

b) combining said IRS-containing specimen with an affinity reagent, capturing said analyte and said IRS with the affinity reagent and isolating said analyte and said IRS by releasing them from the affinity reagent, wherein said IRS is a modified analyte with shifted molecular weight which binds to said affinity reagent;

c) analyzing and quantifying said analyte wherein analyzing and quantifying ~~comprises~~ consists of using matrix-assisted laser desorption/ionization (MALDI) to resolve distinct signals for said analyte and said IRS to determine the ratio of the analyte signal to the IRS signal.

Claim 33. (currently amended): A method according to claim 31, in which said quantifying step further ~~comprises~~ consists of using working curve analysis.

Claim 40. (previously presented) A method according to claim 33, in which said working curve analysis comprises substeps of:

a) making a plurality of standard preparations, each containing a known but differing concentration of the analyte and each containing a known concentration of IRS;

b) obtaining respective mass spectra of each of the plurality of standard preparations;

c) normalizing each of the mass spectra from the plurality of standard preparations by dividing each mass spectrum by the IRS signal within the mass spectrum;

d) creating a working curve by equating the normalized analyte

signals to the analyte concentration of the plurality of standard preparations;

e) obtaining a mass spectrum for the IRS-containing specimen;

f) normalizing the mass spectrum of the IRS-containing specimen by dividing by the IRS signal within the mass spectrum; and

g) quantifying the concentration of the analyte in the specimen using the working curve.

Claim 48. (currently amended) A method for quantifying a protein in a specimen, said method ~~comprising the steps~~ consisting of:

a) combining said specimen with an internal reference species (IRS) of known concentration, in order to calibrate all subsequent steps; whereby said combination is referred to as an IRS-containing specimen;

b) combining said IRS-containing specimen with an affinity reagent, capturing said protein and said IRS with the affinity reagent and isolating said protein and said IRS by releasing them from the affinity reagent, wherein said IRS is a modified protein with shifted molecular weight which binds to said affinity reagent; and

c) analyzing and quantifying said protein wherein analyzing and quantifying ~~comprises~~ consists of using matrix-assisted laser desorption/ionization (MALDI) to resolve distinct signals for said protein and said IRS to determine the ratio of the protein signal to the IRS signal.

Claim 49. (currently amended) A method according to claim 48, in which said quantifying step further ~~comprises~~ consists of using working curve analysis.

Claim 50. (previously presented) A method according to claim 49, in which said working curve analysis comprises substeps of:

a) making a plurality of standard preparations, each containing a known but differing concentration of the protein and each containing a known concentration of IRS;

b) obtaining respective mass spectra of each of the plurality of standard preparations;

c) normalizing each of the mass spectra from the plurality of standard preparations by dividing each mass spectrum by the IRS signal within the mass spectrum;

d) creating a working curve by equating the normalized protein signals to the protein concentration of the plurality of standard preparations;

e) obtaining a mass spectrum for the IRS-containing specimen;

f) normalizing the mass spectrum of the IRS-containing specimen by dividing by the IRS signal within the mass spectrum; and

g) quantifying the concentration of the protein in the specimen using the working curve.

Appellant's amended claim 31 after final contains, and is limited to, 3 method steps. The last method step is the step of analyzing and quantifying the analyte where analyzing and quantifying contain the step of using MALDI. Appellant's amended claim 33 further includes the step of using a working curve analysis in the quantifying step of claim 31. Although the Examiner is correct in that Appellant should have amended independent claim 33 to include using a working curve analysis after the "consisting of" language in step "c" of claim 33, the amendments made to claim 33 alone do not raise any 35 USC 112 issues and therefore Appellant's amendments made to claim 33 after final should have been allowed to be considered on appeal. This same issue repeats itself with respect to Appellant's claim 49. However, in that the amendments made to Appellant's independent claim 48 alone do not raise any 35 USC 112 issues, Appellant's amendments made to claim 48 after final should have been allowed to be considered on appeal.

Further, with respect to claim 40, the "comprising of" language with respect to further defining the use of a working curve is appropriate even if quantifying step of claim 31 is limited

to using MALDI and a working curve analysis.

B. <u>The Examiner Has Not Established a *Prima Facie* Case of Obviousness.</u>

The Examiner has the initial burden to establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, the Examiner must establish that: (1) the prior art reference (or the references when combined) teaches or suggests all the elements of Appellant's claims; and (2) there is some suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine or modify the references. In the present case, the Examiner has failed to establish that the Duncan and Nuwaysir references or the Duncan and Hutchens references recite all of the claim elements including, *inter alia*, the exclusive steps of capturing the analyte and an internal reference species (IRS) with an affinity reagent, releasing the analyte and IRS from the affinity reagent, and then analyzing and quantifying the analyte using matrix-assisted laser desorption/ionization (MALDI) on the released analyte and IRS. The sample does not undergo any additional prior clean-up or purification such as affinity chromatography as disclosed in Nuwaysir. Moreover, there is no suggestion in any of the prior art references cited by the Examiner (or elsewhere in the prior art) to combine or modify the references to achieve Appellant's claims. Thus, the Examiner has failed to establish a *prima facie* case of obviousness for Applicants' claims.

To establish a *prima facie* case of obviousness, the Examiner must show either how the prior art references suggest, either expressly or impliedly, the combination that results in Appellant's claims or, alternatively, the Examiner must present a convincing line of reasoning as to why one skilled in the art would have found the claims to have been obvious in light of the teachings of the references. <u>*Ex parte Clapp*</u>, 227 U.S.P.Q. 972, 973 (Bd. of Pat. Appeals and Interferences, 1985). When the motivation to combine the teachings of the prior art references is not immediately apparent, it is the duty of the Examiner to explain why the combination of the teachings is proper. <u>*Ex parte Skinner*</u>, 2 U.S.P.Q.2d 1788 (Bd. of Pat. Appeals and Interferences, 1986). Significantly, the fact that references <u>can</u> be combined or modified does not render the

resultant combination obvious unless the prior art suggests the desirability of the combination. *In re Mills*, 916 F.2d 680 (Fed. Cir., 1990). The teaching or suggestion to make a claimed combination must be found in the prior art and must not be based on Appellant's disclosure. *In re Vaeck*, 947 Fed.2d 488 (Fed. Cir., 1991).

The test of obviousness is not whether features of a secondary reference may be bodily incorporated into a primary reference's structure, nor whether a claimed invention is expressly suggested in any one or all of the references. Instead, the test is what the combined teachings of references would have suggested to those of ordinary skill in the art. *In re Keller, Terry, and Davies*, 208 U.S.P.Q. 871, 881 (C.C.P.A., 1981). The mere fact that the prior art may be modified to reflect features of the claimed invention does not make the modification, and hence the claimed invention, obvious unless the desirability of such a modification is suggested by the prior art. The claimed invention cannot be used as an instruction manual or "template" to piece together teachings of the prior art so that the claimed invention is rendered obvious. *In re Fritsch*, 23 U.S.P.Q.2d 1780, 1783-84 (C.A.F.C., 1992).

The Examiner first rejected claims 31, 33, 40 and 48-50 under 35 U.S.C. §103(a) as being unpatentable over Duncan (Duncan, M.W. et al., Rapid Communications in Mass Spectrometry, 7:1090-1094, 1993) in view of Nuwaysir (Nuwaysir, L.M. et al. J. Am. Soc. Mass Spectrom., 4:662-669, 1993). In particular, the Examiner states that Duncan teaches the use of internal standards where the internal standards may be isotopically labeled analogues of an analyte (which falls within applicants' claim limitation of "modified analyte with shifted molecular weight") to overcome the difficulties of using MALDI for quantitative analysis of analytes. The Examiner further stated that Duncan also teaches that "real" samples require prior clean-up by, for example, immunoaffinity separation or chromatography. Further, although the Examiner conceded that Duncan fails to demonstrate the method with real samples using any type of affinity reagent, the Examiner points out that Nuwaysir teaches a method of using metal-ion affinity chromatography to purify samples before they are analyzed by MALDI. Accordingly, the Examiner contends that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Duncan on the use of

isotopically labeled internal reference standards for quantification with MALDI with those of Nuwaysir on the use of affinity chromatography for the purification of samples prior to MALDI. The Examiner further states that motivation to combine the teachings is provided by Duncan, which demonstrates the advantages of using internal standards when one wants to quantify an analyte, and Nuwaysir, which teaches that prior purification of samples with affinity chromatography is necessary for mass spectrometry of samples with a large number of peptides. Applicants respectfully traverse this rejection.

Applicants have amended their claims by further limiting the claim language to show that quantification of the analyte is done by capturing the analyte and an internal reference species (IRS) with an affinity reagent, releasing the analyte and IRS from the affinity reagent, and then analyzing and quantifying the analyte using matrix-assisted laser desorption/ionization (MALDI) on the released analyte and IRS. The sample does not undergo any additional prior clean-up or purification such as affinity chromatography as disclosed in Nuwaysir. Accordingly, since neither Duncan nor Nuwaysir, either alone or in combination, disclose Applicants' discrete steps for quantifying an analyte in a specimen, then Applicants' claimed method cannot be obvious in light of Duncan and Nuwaysir.

The Examiner has also rejected claims 31, 33, 40, 48, 49 and 50 under 35 U.S.C. §103(a) as being unpatentable over Duncan in view of Hutchens, U.S. Patent No. 6,528,320 (hereafter "Hutchens"). In particular, the Examiner states that Duncan teaches the use of internal standards where the internal standards may be isotopically labeled analogues of an analyte (which falls within applicants' claim limitation of "modified analyte with shifted molecular weight") to overcome the difficulties of using MALDI for quantitative analysis of analytes. The Examiner further stated that Duncan also teaches that "real" samples require prior clean-up by, for example, immunoaffinity separation or chromatography. Further, although the Examiner conceded that Duncan fails to demonstrate the method with real samples using any type of affinity reagent, the Examiner points out that Hutchens teaches a method of capturing an analyte form a sample on a sample presenting surface derivatized with an affinity reagent that binds the analyte, wherein the affinity reagent is a metal ion, a protein, a peptide, a nucleic acid or a dye,

followed by detecting the captured analyte by laser desorption/ionization mass spectrometry. Therefore, the Examiners contends that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Duncan on the use of isotope-labeled internal standards for quantification with MALDI with those of Hutchens on the use of affinity reagents for the purification of samples prior to MALDI. The Examiner further states that the motivation to combine the teachings is provided by Duncan, which demonstrates the adavantages of using internal standards when one wants to quantify an analyte, and by Hutchens, which teaches that prior purification of samples with an affinity reagent is necessary for mass spectrometry of samples. Applicants respectfully traverse this rejection.

Hutchens et al. discloses a mass spectrometer probe or other sample presenting surface and a method of using the probe or surface for desorption and ionization of analytes. The probe or presenting surface includes a layer of energy absorbing molecules and/or affinity directed analyte capture devices on its surface that are free of analyte and analyte is then applied to the probe or presenting surface. The analyte can be desorbed by a high energy source and detected in the mass spectrometer. Clearly, Hutchens et al. teaches putting media and captured analyte onto a probe tip or presenting surface and then conducting mass spectrometry. In contrast, Applicants sample on which mass spectrometry is conducted does not include an affinity reagent. Instead, Applicants' claims are directed to capturing an analyte species and an internal reference species (IRS) with an affinity reagent, releasing the isolated analyte species and IRS from the affinity reagent, and then detecting the presence of the isolated and released analyte species and IRS using mass spectrometry. Accordingly, since neither Duncan nor Hutchens, either alone or in combination, disclose Applicants' discrete steps for quantifying an analyte in a specimen, then Applicants' claimed method cannot be obvious in light of Duncan and Hutchens.

Further, in that Appellant's claim amendments made after final rejection were directed to excessively limiting the scope of Appellant's method claims, and in that Appellant's previous amendments and responses contained limitations and language which made it clear with respect to what Appellant was trying to claim, Appellant contends that the proposed amendments made

after final did not raise any new issues that would have required further consideration and/or search. Moreover, Appellant contends that the amendments filed just prior to the issuance of the Examiner's final rejection did not necessitate the Examiner's new grounds of rejection that were issued in the Examiner's final office action.

C. The Examiner Has Not Established a *Prima Facie* Case of Obviousness By a Preponderance of the Evidence.

As mentioned above, the Examiner has the initial burden of factually supporting a *prima facie* case of obviousness. This has not been done. Additionally, the Examiner must prove her case by a preponderance of the evidence, with due consideration to the persuasiveness of any arguments in rebuttal. In re Attacher, 977 F.2d 1443 (Fed. Cir., 1992). When the motivation to combine the teachings of the prior art references is not immediately apparent, it is the duty of the Examiner to explain why the combination of the teachings is proper. Ex parte Skinner, 2 U.S.P.Q.2d 1788 (Bd. of Pat. Appeals and Interferences, 1986). Moreover, the fact that references can be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination and/or modification. In re Novo, 916 F.2d 680 (Fed. Cir., 1990). Furthermore, the Examiner cannot suggest the combination or modification based on hindsight reconstruction.

As shown above, the Examiner has failed to meet her burden of persuasion. The Examiner did not identify any express or implied suggestion in either the Duncan, Nuwaysir, or Hutchens references (or anywhere else) to combine or modify the references. Furthermore, although the Examiner stated why she believed it would be obvious to one skilled in the art to combine the Duncan and Nuwaysir references and to combine the Duncan and Hutchens references, such a combination would not arrive at Appellant's method because neither reference discloses quantification of an analyte or protein using the exclusive steps outlined in Appellant's claims. Instead, the references require additional purification steps and/or the mass spectrometry of the affinity agent that is added to the analyte or protein to be quantified. Therefore, the Examiner failed to provide a "convincing line of reasoning". Instead, the Examiner's suggestion and modification of the combined references resulted in quintessential hindsight reconstruction.

Therefore, because the Examiner did not establish by a preponderance of the evidence a *prima facie* case of obviousness, Appellant respectfully submits that the associated rejections of Claims 31, 33, 40 and 48-50 under 35 U.S.C. § 103(a) should be withdrawn.

VIII. CONCLUSION

For the above reasons, Claims 31, 33, 40, and 48-50 are not obvious to one skilled in the art having knowledge of the Duncan, Nuwaysir, and Hutchins references. Accordingly, Appellant respectfully submits that Claims 31, 33, 40 and 48-50 are patentable over the prior art and respectfully requests this Board to so indicate.

Applicants authorize and respectfully request that any fees due be charged to Deposit Account No. 19-2814.

Dated: March 12, 2007

Respectfully submitted,

By _____
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IX. CLAIMS APPENDIX

31. A method for quantifying an analyte in a specimen, said method comprising the steps of:

a) combining said specimen with an internal references species (IRS) of known concentration, in order to calibrate all subsequent steps; whereby said combination is referred to as an IRS-containing specimen;

b) combining said IRS-containing specimen with an affinity reagent, capturing and isolating said analyte and said IRS, wherein said IRS is a modified analyte with shifted molecular weight which binds to said affinity reagent;

c) analyzing and quantifying said analyte wherein analyzing and quantifying comprises using matrix-assisted laser desorption/ionization (MALDI) to resolve distinct signals for said analyte and said IRS to determine the ratio of the analyte signal to the IRS signal.

33. A method according to claim 31, in which said quantifying step further comprises working curve analysis.

40. A method according to claim 33, in which said working curve analysis comprises substeps of:

a) making a plurality of standard preparations, each containing a known but differing concentration of the analyte and each containing a known concentration of IRS;

b) obtaining respective mass spectra of each of the plurality of standard preparations;

c) normalizing each of the mass spectra from the plurality of standard preparations by dividing each mass spectrum by the IRS signal within the mass spectrum;

d) creating a working curve by equating the normalized analyte

signals to the analyte concentration of the plurality of standard preparations;

e) obtaining a mass spectrum for the IRS-containing specimen;

f) normalizing the mass spectrum of the IRS-containing specimen by dividing by the IRS signal within the mass spectrum; and

g) quantifying the concentration of the analyte in the specimen using the working curve.

48. A method for quantifying a protein in a specimen, said method comprising the steps of:

a) combining said specimen with an internal reference species (IRS) of known concentration, in order to calibrate all subsequent steps; whereby said combination is referred to as an IRS-containing specimen;

b) combining said IRS-containing specimen with an affinity reagent, capturing and isolating said protein and said IRS, wherein said IRS is a modified protein with shifted molecular weight which binds to said affinity reagent; and

c) analyzing and quantifying said protein wherein analyzing and quantifying comprises using matrix-assisted laser desorption/ionization (MALDI) to resolve distinct signals for said protein and said IRS to determine the ratio of the protein signal to the IRS signal.

49. A method according to claim 48, in which said quantifying step further comprises working curve analysis.

50. A method according to claim 49, in which said working curve analysis comprises substeps of:

a) making a plurality of standard preparations, each containing a known but differing concentration of the protein and each containing a known concentration of IRS;

b) obtaining respective mass spectra of each of the plurality of

standard preparations;

c) normalizing each of the mass spectra from the plurality of standard preparations by dividing each mass spectrum by the IRS signal within the mass spectrum;

d) creating a working curve by equating the normalized protein signals to the protein concentration of the plurality of standard preparations;

e) obtaining a mass spectrum for the IRS-containing specimen;

f) normalizing the mass spectrum of the IRS-containing specimen by dividing by the IRS signal within the mass spectrum; and

g) quantifying the concentration of the protein in the specimen using the working curve.

X. EVIDENCE APPENDIX

None

XI. RELATED PROCEEDINGS APPENDIX

None – related appeal is still pending